

PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)
(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference 150381/KB | FOR FURTHER ACTION | |
| See Form PCT/A/PEA/416 | | |
| International application No. PCT/CZ2004/000050 | International filing date (day/month/year) 24.08.2004 | Priority date (day/month/year) 26.08.2003 |
| International Patent Classification (IPC) or national classification and IPC C07D491/22 | | |
| Applicant PLIVA-LACHEMA A.S. et al. | | |
| <p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> <i>(sent to the applicant and to the International Bureau)</i> a total of sheets, as follows:</p> <ul style="list-style-type: none"> <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. <p>b. <input type="checkbox"/> <i>(sent to the International Bureau only)</i> a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> | | |
| <p>4. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Box No. I Basis of the opinion <input type="checkbox"/> Box No. II Priority <input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input checked="" type="checkbox"/> Box No. VII Certain defects in the international application <input type="checkbox"/> Box No. VIII Certain observations on the international application | | |

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| Date of submission of the demand 21.03.2005 | Date of completion of this report 19.05.2005 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Deutsch, W Telephone No. +49 89 2399-4465 |

INTERNATIONAL PRELIMINARY REPORT
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
 - international search (under Rules 12.3 and 23.1(b))
 - publication of the international application (under Rule 12.4)
 - international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):
 - a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

Description, Pages

1-4 as originally filed

Claims, Numbers

1-5 as originally filed

3. The amendments have resulted in the cancellation of:
 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):
4. This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|-----|
| Novelty (N) | Yes: Claims | 1-5 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | 1-5 |
| | No: Claims | |
| Industrial applicability (IA) | Yes: Claims | 1-5 |
| | No: Claims | |

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

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V

IAP20 Rec'd PCT/PTO 07 FEB 2006

Reference is made to the following documents:

- D1: SAWADA, SEIGO ET AL.: "Synthesis and antitumor activity of 20(S)-camptothecin derivatives: carbamate-linked, water soluble derivatives of 7-ethyl-10-hydroxycamptothecin" CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 39, no. 6, 1991, pages 1446-1454, XP002306175
- D2: US-B-6 235 9071 (HENEGAR KEVIN E ET AL) 22 May 2001 (2001-05-22)
- D3: US-A-4 604 463 (SUGINO EIICHI ET AL) 5 August 1986 (1986-08-05)
- D4: WO 96/31513 A (UPJOHN CO ; HENEGAR KEVIN E (US); SIH JOHN C (US)) 10 October 1996 (1996-10-10)

Novelty

The compounds of the present application differ from those disclosed in D1 - D4 through the use of dimethylamino pyridine.

Inventive Step

The closest prior art considered to be D1, D2 (see column 23) or D3 (see example 4c).

The only difference between the process of the present claims and those of D1-D3 is the use dimethylaminopyridine for the reaction of the compounds of formula II and III in place of pyridine.

The skilled person would have readily considered replacing pyridine by dimethylaminopyridine (qualitative) and through the polar aprotic solvent.

The problem underlying the invention is provision of a further process for the preparation of irinotecan base having surprising effects compared to the closest prior art.

The present process allows simpler "work ups" compared to the processes of the prior art

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involving pyridine and gives rise to considerably higher yields than the prior art processes (cf page 2, line 6 in the description of the present application and example 1 of the application). The skilled person would not have considered that dimethylaminopyridine and polar aprotic solvent could be used to achieve these effects, such that an inventive step may be acknowledged.

VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 are not mentioned in the description, nor is/are these documents identified therein.

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